

**REMARKS**

Reconsideration of the present application is requested in view of the foregoing amendments and the following remarks.

**I. Claim Amendments**

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

It is acknowledged that the foregoing amendments are submitted after final rejection of the claims. However, because the amendments do not introduce new matter, and either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

Claims 14 and 23 are amended to further prosecution of the application. Claim 14 has been amended to correct a typographical error. Claim 23 has been amended to recite:

- ...
- b) coating of the layer containing the plant substance on the neutral core is performed by powder-coating including spraying an alcoholic solution of polyvinylpyrrolidone as a binder when the plant substance is in the form of a dry extract, or by coating in solution including spraying an alcoholic solution of polyvinylpyrrolidone as a binder when the plant substance is in the form of a soft or fluid extract; and
  - c) during the method, 5 to 25 % by weight of organic solvents are used.

Support for this amendment is provided in the specification, for example, at paragraphs [0038]-[0040] and example 5, which recite:

[0038] According to the process of the invention, the granules are obtained by powder-coating when the plant substance is in the form of a dry extract.

[0039] Powder-coating is advantageously carried out by alternately spraying an alcoholic or aqueous-alcoholic solution of a binder, and the dry extract.

[0040] In the case of a fluid extract, the active layer may be coated with a layer obtained by spraying a solution of binder. The fluid extract preferably contains about 30 to 40 % of alcohol.

Example 5 : "The Neutres are introduced into the tank and the fluid extract is sprayed in fractions. The granules are sized by sieving and then dried under an air bed. A solution of polyvinylpyrrolidone in alcohol is then applied. The granules are again sieved and dried, and then lubricated with talc."

After entry of the foregoing amendments, claims 14, 16-20, and 23-25 are pending in the application.

## **II. Claim Objections**

Claim 14 was objected to as being dependent upon a cancelled claim. As amended, claim 14 depends from claim 23. Withdrawal of the objection is requested.

### III. Claim Rejections - 35 U.S.C. § 112

Claims 23, 14, 16-20, 24 and 25 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly “as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.” The Applicants traverse the rejection in view of the foregoing amendments and for the following reasons.

Claim 23 was rejected for reciting “the process,” allegedly without antecedent basis. Claim 23 has been amended to recite “the method.” Because claim 23 relates to “a method for preparing granules containing a plant substance,” there is antecedent basis for “the method.”

Claim 23 is rejected for reciting the term “soft,” allegedly because the term “is a relative term which render the claim indefinite.” The Applicants previously responded to this rejection in an Amendment and Response dated May 11, 2004. The rejection was not addressed in the subsequent Office Action dated September 8, 2004.

In previously responding to this rejection, the Applicants provided pages 858-859 of the European Pharmacopoeia 3<sup>rd</sup> Edition (1997), and pages 1782-1783 of the British Pharmacopoeia (2001). The British Pharmacopoeia (2001) states that “Extracts comply with the requirements of the 3<sup>rd</sup> edition of the European Pharmacopoeia.” (*See* British Pharmacopoeia, column 1, page 1, paragraph entitled “Extracts.”) These pharmacopoeias state:

*Soft extracts* are preparations of an intermediate consistency, between liquid and dry extracts. They are obtained by partial evaporation of the solvent used for preparation. Only ethanol of suitable concentration or water is used. *Soft extracts* generally have a dry residue of not less than 70 per cent by mass. They may contain suitable anti-microbial preservatives.

(See European Pharmacopoeia column 1, page 859, paragraph entitled “Extraits mous ou fermes” (emphasis added), and British Pharmacopeia, column 1, page 1783, paragraph entitled “Soft Extracts” (emphasis added).) As such, the meaning of the term “soft extract” was known in the art at the time the application was filed. One skilled in the art would understand the metes and bounds of the claims.

Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph, are requested.

#### **IV. Claim Rejections - 35 U.S.C. § 103**

Claims 14, 16-20, and 23-25 stand rejected under 35 U.S.C. § 103 as being unpatentable over Kamada *et al.* (U.S. 5,384,130) in view of Menzi *et al.* (U.S. 6,056,949) and Makino *et al.* (U.S. 5,026,560). As such, the claims stand rejected as allegedly obvious in view of the combined teachings of three (3) references. The Applicants respectfully traverse the rejection.

##### **A. Claim Amendments**

The Applicants’ previous arguments with respect to the rejection were not deemed persuasive. In particular, the Office Action states that “the claims are not strictly limited to the use of organic solvent.” As amended, part b) of claim 23 recites that “spraying an alcoholic solution of polyvinylpyrrolidone” is performed “when the plant substance is in the form of a dry extract” or “when the plant substance is in the form of a soft or fluid extract.” In addition, part c) recites that “during the method, 5 to 25 % by weight of organic solvents are used.” Reconsideration of the Applicants’ previous arguments is requested in view of the claim amendments.

##### **B. Kamada *et al.***

The Office Action dated June 7, 2005, states that the primary reference, Kamada *et al.*, fails to teach “the use of a plant substance containing extracts in his coating solutions.” As such, Kamada *et al.* does not anticipate the claimed methods.

Further, the Applicants previously indicated that Kamada *et al.* does not teach or suggest a method that utilizes an organic solvent. However, the present Office Action indicates that Kamada *et al.* “never states that the coating must be solvent-free aqueous suspensions [and that] many aqueous suspensions can contain organic solvents such as ethanol or ethylene glycol.” It is respectfully noted that a reference does not anticipate or render obvious claimed subject matter based on elements that the reference might possibly include. Rather, in order to anticipate or render obvious claimed subject matter, a reference must teach or suggest elements meeting each limitation of the claims. Kamada *et al.* does not teach or suggest a method that utilizes an organic solvent. In particular, Kamada *et al.* does not teach or suggest a method that includes “spraying an alcoholic solution of polyvinylpyrrolidone as a binder.”

In fact, Kamada *et al.* teaches away from methods that include the use of an organic solvent. With respect to the use of an organic solvent, Kamada *et al.* states that

The use of an organic solvent **brings problems** relating to environmental pollution, cost, residues and the like. Thus, these organic solvents will be gradually replaced by aqueous solutions or suspensions.

(See Kamada *et al.*, col. 2, lines 7-11 (emphasis added).) Therefore, Kamada *et al.* indicates that there are **problems** associated with the use of organic solvent. As a solution, Kamada *et al.* states that “the present invention provides a process for the production of the spherical granules...using a pharmacologically **aqueous binder solution**, and **spraying an aqueous solution or suspension** of a coating agent to form spherical granules....” (See Kamada *et al.*, col. 2, lines 50-57 (emphasis added).) Clearly, Kamada *et al.* indicates that the use of organic solvents is disfavored. Accordingly, the entire specification of Kamada *et al.* is related to methods that utilize binder solutions that are free of organic solvent (*i.e.*, “solvent free”).

With respect to seed cores, Kamada *et al.* states that

Nevertheless, in a process for the preparation of a pharmaceutical wherein ***seed cores composed of sucrose or sucrose/starch*** are coated with a powder containing an active ingredient, using a binder aqueous solution, and further coated by spraying an aqueous solution or suspension of a coating agent, ***certain problems arise***. For example, sucrose, which is a main ingredient of the seed cores, is dissolved, the surface of the seed cores becomes tacky, and the seed cores exhibit a high friability. ***These problems cause disadvantages***, such as aggregation of granules, adhesion of granules to a wall of a coating machine, and a lowered yield. Moreover, the resulting granules have a problem in that the dissolution rate of the active ingredient from the granules is lowered with the passage of time. Further, upon administration, since sucrose, a main ingredient of the seed cores, is gradually dissolved. This results in a reduction of the strength of the granules. An intestinal movement may therefore break the coating of the granules. Since this coating is intended to control the dissolution of the active ingredient, ***a highly undesirable dissolution profile may appear***.

(See Kamada *et al.*, col. 2, lines 12-33 (emphasis added).) Therefore, in addition to problems associated with the use of organic solvents, Kamada *et al.* further indicates that there are ***problems*** with using “seed cores composed of sucrose or sucrose/starch.”

Continuing, Kamada *et al.* state that “[t]he present inventor surprisingly found that the ***various above-mentioned problems*** can be resolved by providing pharmacologically inactive spherical seed cores ***containing at least 50% of microcrystalline cellulose*** having an average degree of polymerization of between 60 and 375.” (See Kamada *et al.*, col. 2, lines 36-41 (emphasis added).) Throughout the specification, Kamada *et al.* emphasizes that the seed cores contain at least 50 % microcrystalline cellulose. (See, e.g., Kamada *et al.*, col. 2, lines 42-45 and col. 2, lines 64-68).

Therefore, Kamada *et al.* indicate that the “various above-mentioned problems” include use of an organic solvent and use of seed cores composed of sucrose or sucrose/starch. As a solution to the “various above-mentioned problems,” Kamada *et al.* proposes use of an ***aqueous binding solution*** (*i.e.*, a “solvent-free” binding solution) and ***seed cores containing at least 50% of microcrystalline cellulose***. Accordingly, all the Examples of Kamada *et al.* utilize solvent-free binder solutions and microcrystalline cellulose seed cores.

The Office Action indicates that “Applicant’s arguments directed to the use of microcrystalline cellulose by Kamada are not commensurate with the scope of the claims.” However, the Applicants’ arguments directed to the use of microcrystalline cellulose by Kamada *et al.* are ***directly related*** to whether one of skill in the art ***would not be motivated*** to combine Kamada *et al.* with any reference that does not teach: (1) the use of microcrystalline cellulose cores containing at least 50% of microcrystalline cellulose; and (2) the use of a solvent-free binding solution. A *prima facie* case of obviousness requires that there be motivation to combine cited references. It is improper to use the present application as the motivation to combine the cited references.

C. Menzi *et al.*

The Office Action dated June 7, 2005, states that “Menzi does not explicitly use a PVP binder.” Accordingly, Menzi *et al.* does not teach or suggest “spraying an alcoholic solution of polyvinylpyrrolidone as a binder” as recited in the present claims. However, Menzi *et al.* is cited as a secondary reference in combination with Kamada *et al.*

There is no motivation to combine the teachings of Menzi *et al.* with Kamada *et al.* With respect to Menzi *et al.*, the Office Action dated June 7, 2005, states that “Menzi’s core is mainly of carbohydrates (such as starch, sucrose, lactose or maltodextrin).” However, one of skill in the art would not be motivated to combine the teachings of Menzi *et al.* with Kamada *et al.*, where “Menzi’s core is mainly of carbohydrates (such as starch, sucrose, lactose or maltodextrin).” Kamada *et al.* discusses ***problems*** associated with the use of cores that include sucrose or sucrose/starch (see Kamada *et al.*, col. 2, lines 12-33) and provides

***solutions to the problems*** that do not involve the use of cores that include sucrose or sucrose/starch (see e.g., Kamada *et al.*, col. 2, lines 42-45 and col. 2, lines 64-68).

Furthermore, the Office Action dated June 7, 2005, states that “Menzi also teaches water and ethanol as their solvent of choice.” However, one of skill in the art would not be motivated to combine the teachings of Menzi *et al.* with Kamada *et al.*, where Menzi teaches “water and ethanol as their solvent of choice.” Kamada *et al.* discusses ***problems*** associated with the use of organic solvents (see Kamada *et al.*, col. 2, lines 7-11) and provides ***solutions to the problems*** that do not involve the use of organic solvent (see Kamada *et al.*, col. 2, lines 50-57).

D. Makino *et al.*

The Office Action dated June 7, 2005, states that “Makino fails to explicitly use a drug from a plant source.” Accordingly, Makino *et al.* does not teach or suggest coating a layer containing a plant substance on a neutral core “including spraying an alcoholic solution of polyvinylpyrrolidone as a binder,” as recited in the present claims. However, Makino *et al.* is cited as a secondary reference in combination with Kamada *et al.* and Menzi *et al.*

There is no motivation to combine the teachings of Makino *et al.* with Kamada *et al.* With respect to Makino *et al.*, the Office Action dated June 7, 2005, states “Makino is used to show the typical ranges of sucrose and starch in a neutral core.” However, one of skilled in the art would not be motivated to combine the teachings of Makino *et al.* with Kamada *et al.*, where Makino is used to show the typical ranges of sucrose and starch in a neutral core. Kamada *et al.* discusses ***problems*** associated with the use of cores that include sucrose or sucrose/starch (see Kamada *et al.*, col. 2, lines 12-33) and provides ***solutions to the problems*** that do not involve the use of cores that include sucrose or sucrose/starch (see e.g., Kamada *et al.*, col. 2, lines 42-45 and col. 2, lines 64-68).



E. Summary

Therefore, none of the cited references teach or suggest elements meeting all the limitations of the claims as amended. Furthermore, one of skill in the art would not be motivated to combine the cited references to render obvious the subject matter of the claims as amended. For all these reasons, the claimed method is not obvious in view of the cited references.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103 are respectfully requested.

V. Conclusion

The Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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